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APPEAL BRIEF

PETITION FOR EXTENSION OF TIME

TITLE:	**Apparatus and Process to Produce Particles Having a Narrow Size Distribution and Particles Made Thereby**
U.S. SERIAL NO.:	**09/919,278**
FILING DATE:	**July 31, 2001**
INVENTOR:	**Snyder, et al.**
EXAMINER:	**Gollamudi S. Kishore**
GROUP ART UNIT:	**1615**
CONFIDENTIALITY NOTE:	**4703**

PATENT
Atty. Dkt. No. NEKT/0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Snyder, et al.

Serial No.: 09/919,278

Confirmation No.: 4703

Filed: July 31, 2001

For: Apparatus and Process to Produce Particles Having a Narrow Size Distribution and Particles Made Thereby

Group Art Unit: 1615

Examiner: Gollamudi S. Kishore

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Commissioner for Patents
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June 13, 2007 — Date
John-Paul F. Cherry

Dear Sir:

APPEAL BRIEF

The Applicant submits this Appeal Brief to the Board of Patent Appeals and Interferences on appeal from the decision of the Examiner of Group Art Unit 1657 dated 11/13/2006, finally rejecting claims 19-32. The final rejection of claims 19-31 is appealed. This Appeal Brief is believed to be timely since it is filed by the due date extended one month to June 13, 2007, as set by the filing of a Notice of Appeal on March 13, 2007. A Request for an Extension of Time providing authorization for fees is attached herewith. The Commissioner is hereby authorized to charge counsel's Deposit Account No. 20-0782/NEKT/0002/JPC the fee of $500.00 for the filing of this Appeal Brief, and for any additional fees required to make this Response timely and acceptable to the Office.

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REAL PARTY IN INTEREST

The real party in interest is Nektar Therapeutics, located at 150 Industrial Road, San Carlos, California 94070.

RELATED APPEALS AND INTERFERENCES

The Applicant asserts that no other appeals or interferences are known to the Applicant, the Applicant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 19-32 are pending in the application. Claims 1-31 were originally presented in the application. Claim 32 was added during prosecution. Claims 1-18 have been cancelled without prejudice. Claims 19-32 stand finally rejected as discussed below. The final rejections of claims 19-31 are appealed. The pending claims are shown in the attached Claims Appendix.

STATUS OF AMENDMENTS

All claim amendments have been entered by the Examiner. No amendments to the claims were proposed after the final rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

Claimed embodiments of the invention provide a method for spray drying a feed stock containing a pharmaceutical agent. In the embodiment of independent claim 19, a method for spray drying a feed stock containing a pharmaceutical agent to produce particles suitable for pulmonary administration having a narrow particle size distribution includes the steps of providing a liquid feed stock comprising a pharmaceutically active agent selected from a list of active agents (page 6, line 33 – page 7, line 15), forcing the liquid feed stock into a manifold defined between a vibratable element (54) and a plate (61) and forcing the feed stock through the plate, the plate comprising holes (62) of at least one predetermined diameter, in order to produce liquid droplets (page 13, lines 12-24), drying the droplets in a gas stream (page 14, lines 24-32) to produce dried particles comprising a mass median aerodynamic diameter of less than 10 microns and a particle size distribution wherein at least 70% of the mass of the particles have a diameter within a 4 micron range (page 9, lines 27-31), and collecting said dried particles (page 15, lines 16-18).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 19-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Ketcham et al.* (U.S. Patent No. 4,871,489, hereinafter referred to as *Ketcham*) in view of *Backstrom et al.* (U.S. Patent No. 5,952,008, hereinafter referred to as *Backstrom*) and *Forrester et al.* (U.S. Patent No. 4,590,489, hereinafter referred to as *Forrester*).

ARGUMENTS

Rejection of Claims 19-32 under 35 U.S.C. § 103(a) over *Ketcham* in view of *Backstrom* and *Forrester*

The Examiner bears the initial burden of establishing a *prima facie* case of obviousness. *See* MPEP § 2142. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one ordinary skill in the art to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* MPEP § 2143. The present rejection fails to establish at least the first and third criterions.

The References

Ketcham discloses an apparatus for producing liquid droplets of solutions of metal oxides or metal oxide precursors such as zirconium hydroxynitrate, zirconium acetate, aluminum oxide, and aluminum hydroxynitrate (Abstract and column 8, lines 20-40). The solutions are fed through a feed tube 11 and through an orifice plate 13 (Figure 1 and column 3, lines 59-67). The orifice plate is connected to an orifice cup 14 which is in active engagement with a vibratory element 15. The vibratory element 15 causes the orifice plate to vibrate and is located away from the flow of the liquid feed. The droplets are dried in an inert dilution gas to form metal oxide precursor particles which have a number mean size of less than 5 microns, and more preferably less than about 2 microns (column 8, line 62 – column 9, line 16).

Backstrom discloses a pharmaceutical composition including a mixture of active compounds, a pharmaceutically active polypeptide, and an enhancer compound (Abstract). *Backstrom* further discloses that the active compounds should consist of particles having a diameter less than approximately 10 μm (e.g., between 0.01-10 μm, and ideally between 1-6 μm) (column 1, lines 41-46). The small particle diameters are

obtained through micronizing the mixture in a suitable mill, such as a jet mill (column 8, lines 34-38).

Forrester discloses particles of inhalation drugs made by spray drying and prefers that more than 90% of the particles of the active compound be less than 60 μm, and especially less than 10 μm in diameter (column 5, lines 52-58). *Forrester* particularly prefers at least 50% of the particles to be of 2 to 6 in diameter. However, in the only example of small particle sizes, an average mass mean diameter of 11 μm was obtained (column 15, lines 65-66).

The Examiner's Argument

Regarding claim 19, the Examiner argues that the *Ketcham* discloses an apparatus and process for producing liquid droplets having a narrow size distribution, wherein this liquid streams are forced under pressure through a plurality of orifices in an orifice plate wherein the thin liquid streams are vibrated to cause the breakup of each stream Into droplets having a narrow size distribution, a vibrating members and a separate plate comprising holes. The Examiner relies on *Backstrom* and *Forrester* as disclosing pharmaceutically active agents such as a mixture of active compounds and a pharmaceutical active polypeptide, the mixture being in the form of a dry powder for inhalation in which the primary particles having a diameter less than or equal to about 10 microns. The Examiner asserts that the combination of *Ketcham*, *Backstrom*, and *Forrester* discloses all the limitations of the Applicant's claims, and that the Applicant's claims differ from the combination of *Ketcham*, *Backstrom*, and *Forrester* only in the specific percentages and the size of diameter range selected for the particles. The Examiner asserts that it would have been prima facie obvious to one having ordinary skill in the art at the time of invention to select any of the apparatuses, processes, and pharmaceutical active agents as from the cited references.

The Applicant's Response to the Examiner's Argument

Respectfully, the Applicant submits the combination of *Ketcham*, *Backstrom*, and *Forrester* fails to teach all the limitations of the Applicant's claims. For example, the combination of *Ketcham*, *Backstrom*, and *Forrester* does not teach, show, suggest, or otherwise make obvious forcing the liquid feed stock into a manifold defined between a vibratable element and a plate and forcing the feed stock through the plate, said plate comprising holes of at least one predetermined diameter, in order to produce liquid droplets. *Ketcham* does not disclose forcing the liquid feed stock into a manifold defined between a vibratable element and a plate. *Ketcham* discloses forcing the liquid feedstock through a feed tube (11) and into a chamber (10) defined between a base (18) and an orifice plate (13) (Figure 1). The orifice plate (13) is integrally connected to liquid an orifice cup (14), which in turn is in operative engagement with a vibratory element (15) (figure 1 and column 3, lines 64-67). Because the chamber (10) of *Ketcham* is defined between the base (18) and the orifice plate (13), and not between the vibratory element (15) and the orifice plate (13), the combination of *Ketcham*, *Backstrom*, and *Forrester* does not teach, show, suggest, or otherwise make obvious forcing the liquid feed stock into a manifold defined between a vibratable element and a plate, as recited in claim 19 and claims dependent thereon.

Furthermore, the Applicant submits that the combination of *Ketcham*, *Backstrom*, and *Forrester* does not motivate the skilled artesian to derive the claimed invention. *Ketcham* discloses forming particles of metal oxide precursors and remains silent to pharmaceutical compounds as disclosed by *Backstrom* and *Forrester*. Therefore, there is no suggestion obtained in the references, nor would a person of ordinary skill in the art suggest, that combining *Ketcham* with *Backstrom* and *Forrester* would result in the active pharmaceutical compounds of *Backstrom* and *Forrester* to form particles like the inorganic metal precursors recited in *Ketcham*.

The Applicant submits independent claim 19 is allowable, therefore the dependent claims are also believed to be allowable since they further narrow the claim scope.

The Examiner's Response to the Applicant's Arguments

The Applicant now refers to the Examiner's response to the Applicant's arguments of the Examiner's Final Action (pages 2-3, paragraph 2) where the Examiner disagrees with the Applicant's argument that *Ketcham* does not disclose forcing the liquid feed stock into a manifold defined between a vibratable element and a plate and forcing the feed stock through the plate. The Examiner asserts that Figure 1 of *Ketcham* shows that the liquid feed is forced through the plate and the vibrating element, and that the Applicant's claims do no require the presence of the vibratable element to be inside.

However, the Applicant's claims recite forcing the liquid feed stock into a manifold defined between a vibratable element and a plate. As described above, *Ketcham* does not disclose such a manifold defined between a vibratable element and a plate. *Ketcham* discloses forcing the feedstock into the chamber (10), which is defined between the base (18) and the orifice plate (13) (Figure 1). The Examiner asserts that, according to Figure 1, *Ketcham* discloses that the liquid feed is forced through the plate and the vibrating element. The Applicant respectfully traverses this assertion.

As can be seen in Figure 1, the liquid feed is forced into the chamber 14 which is defined between the base (18) and the orifice plate (13) and then forced through the orifice plate (13). Furthermore, as disclosed in Figure 1 and in column 3, lines 64-67, the vibratory element (15) of *Ketcham* does not alone, or coupled with the plate or base, define a manifold into which the liquid feed is forced. Because the prior art references together must teach or suggest all the claim limitations, and because the combination of *Ketcham*, *Backstrom*, and *Forrester* fails to teach or suggest all the claim limitations as discussed above, the Applicant submits that claim 19 and claims 20-31 that depend thereon are patentable over *Ketcham* in view of *Backstrom* and *Forrester*

The Examiner further asserts that the apparatus described in *Ketcham* is for producing particles and that the method would be the same irrespective of whether the particles produced for pharmaceutical purpose or otherwise. However, *Ketcham* discloses forming particles from solutions or suspensions of oxygen-containing materials that are decomposable to a refractory metal oxide. Every example of *Ketcham* discloses a metal and oxygen source, such as zirconium hydroxynitride (examples 1-11), zirconium acetate (examples 12-16), and aluminum chlorohydrate (examples 17-

18). These metal oxides have very different physical and chemical characteristics from the pharmaceutical particles disclosed by *Backstrom* and *Forrester*. *Ketcham* does not suggest that the apparatus of *Ketcham* could be used to produce particles of pharmaceutical compounds. Furthermore, because the metal oxides of *Ketcham* and the pharmaceutical compounds of *Backstrom* and *Forrester* possess very different chemical and physical characteristics a person of ordinary skill in the art would not be motivated or suggest producing particles of pharmaceutical compounds using the apparatus of *Ketcham*. Therefore, there is no suggestion obtained in the references, nor would a person of ordinary skill in the art suggest, that combining *Ketcham* with *Backstrom* and *Forrester* would result in the active pharmaceutical compounds of *Backstrom* and *Forrester* to form particles like the inorganic metal precursors recited in *Ketcham*.

Additionally, *Backstrom* teaches pharmaceutical compositions which are micronized in order to make them suitable for inhalation. The micronization is performed in a suitable mill, such as a jet mill (column 8, lines 34-36), and does not involve the formation of droplets which are dried by a drying gas as in *Ketcham* and *Forrester*. Therefore, there is no motivation found in the references, nor would a person of ordinary skill in the art suggest to combine *Backstrom* with *Ketcham* and *Forrester*.

Thus, the Applicant submits that claim 19 and claims 20-31 that depend thereon are patentable over *Ketcham* in view of *Backstrom* and *Forrester*. Accordingly, the Applicant respectfully requests the rejection be withdrawn and the claims allowed.

CONCLUSION

For the reasons advanced above, the Applicant respectfully urge that the rejection of claims 19-31 as being unpatentable under 35 U.S.C. § 103 is improper. Reversal of the rejection in this appeal is respectfully requested.

Respectfully submitted,

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CLAIMS APPENDIX

1-18. (Cancelled)

19. (Previously Presented) A method for spray drying a feed stock containing a pharmaceutical agent to produce particles suitable for pulmonary administration having a narrow particle size distribution comprising:

providing a liquid feed stock comprising a pharmaceutically active agent selected from the group consisting of insulin, calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporine, granulocyte colony stimulating factor (GCSF), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-2, luteinizing hormone releasing hormone (LHRH), somatostatin, octreotide, vasopressin analog, follicle stimulating hormone (FSH), insulin-like growth factor, insulintropin, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, macrophage colony stimulating factor (M-CSF), nerve growth factor, parathyroid hormone (PTH), thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, interleukin-1 receptor, 13-cis retinoic acid, pentamidine isethionate, albuterol sulfate, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetonide, ipratropium bromide, flunisolide, fluticasone, cromolyn sodium, and ergotamine tartrate;

forcing said liquid feed stock into a manifold defined between a vibratable element and a plate and forcing the feed stock through the plate, said plate comprising holes of at least one predetermined diameter, in order to produce liquid droplets;

drying said droplets in a gas stream to produce dried particles comprising a mass median aerodynamic diameter of less than 10 microns and a particle size distribution wherein at least 70% of the mass of the particles have a diameter within a 4 micron range; and

collecting said dried particles.

20. (Original) A method according to claim 19 wherein the dried particles comprise a particle size distribution wherein at least 80% of the mass of the particles have a diameter within a 4 micron range.

21. (Original) A method according to claim 19 wherein the dried particles comprise a particle size distribution wherein at least 90% of the mass of the particles have a diameter within a 4 micron range.

22. (Original) A method according to anyone of claims 19-21 wherein the dried particles have a diameter within a 3 micron range.

23. (Original) A method according to anyone of claims 19-21 wherein the dried particles have a diameter within a 1.5 micron range.

24. (Currently Amended) A method according to claim 19 further comprising vibrating said vibratable element in order to force said feed stock through the plate and produce droplets.

25. (Original) A method according to claim 24 wherein said plate is vibrated by coupling a piezoelectric element to said plate.

26. (Original) A method according to claim 19 wherein said holes comprise a predetermined diameter of less than 30 microns.

27. (Original) A method according to claim 19 wherein said plate comprises holes having a first diameter of less than 30 microns and a second series of holes having a second diameter of ± 50% of said first diameter.

28. (Original) A method according to claim 27 wherein said second diameter is

within ± 20% of said first diameter.

29. (Original) A method according to claim 28 wherein said first diameter is less than 10 microns.

30. (Original) A method according to claim 19 wherein said particles are porous.

31. (Previously Presented) A method according to claim 19 wherein said particles comprise a mass mean diameter less than 10 microns and a mass median aerodynamic diameter of 1-5 microns.

32. (Previously Presented) A method for spray drying a feed stock containing a pharmaceutical agent comprising:

providing a liquid feed stock comprising a pharmaceutically active agent selected from the group consisting of insulin, calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporine, granulocyte colony stimulating factor (GCSF), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-2, luteinizing hormone releasing hormone (LHRH), somatostatin, octreotide, vasopressin analog, follicle stimulating hormone (FSH), insulin-like growth factor, insulintropin, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, macrophage colony stimulating factor (M-CSF), nerve growth factor, parathyroid hormone (PTH), thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, interleukin-1 receptor, 13-cis retinoic acid, pentamidine isethionate, albuterol sulfate, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetonide, ipratropium bromide, flunisolide, fluticasone, cromolyn sodium,

and ergotamine tartrate;

atomizing said feed stock in order to produce liquid droplets;

drying said droplets in a gas stream to produce dried particles comprising a mass median aerodynamic diameter of less than 10 microns and particle size distribution wherein at least 70% of the mass of the particles have a diameter within a 4 micron range; and

collecting said dried particles.

EVIDENCE APPENDIX

The Applicant state that there is no evidence submitted under 37 C.F.R. §1.130, 1.131 or 1.132, or other evidence entered by the Examiner or relied upon by the Applicant in the Appeal.

RELATED PROCEEDINGS APPENDIX

No copies of decisions rendered by a court or the Board in the related appeal or interference listed on page 4 of this Brief are included as there have been no decisions by the court or the Board in the related appeal or interference listed on page 4 of this Brief.